

## REMARKS

### A. Rejection under 35 U.S.C. 103

Claims 73-74, 142-143, 219-220, 234-235, and 248-249 are rejected under 35 U.S.C. 103 as obvious over Farazi et al. in view of Lightfoot et al. and Roelant et al. According to the Office Action, Farazi et al. teach that mutants of human IMPDH are resistant to inhibitors of wildtype IMPDH, and that mutant IMPDH that are resistant to IMPDH inhibitors can be identified by screening for cells capable of growing in the presence of IMPDH (*note: it appears that this should read MPA*). Based on this, the Office Action states that the only difference between Farazi et al. and the present invention is the mutant IMPDH. The Office Action then goes on to state that wildtype IMPDH and the IMPDH of the present invention (SEQ ID NO:4) differ at residues 190, 191, 333, and 351. The Office Action states, however, that the wildtype IMPDH sequence obtained by Collart et al. was incorrect, and that the wildtype protein actually has an alanine at residue 190 and a glycine at residue 191. Thus, wildtype IMPDH and the IMPDH of the present invention vary only at residues 333 and 351. The Office Action next states that Lightfoot et al. teach an MPA-resistant mouse IMPDH mutant with two point mutations: Thr-333-Ile and Ser-351-Tyr. According to the Office Action, human IMPDH also contains a Thr at residue 333 and a Ser at residue 351, and is highly homologous to murine IMPDH.

Based on this information, the Office Action asserts that a person of ordinary skill in the art would have been motivated to make mutations at residues 333 and 351, expose cells comprising this mutation and control cells to IMPDH inhibitors, and select

cells that are able to grow in the presence of the IMPDH inhibitor using cell proliferation methods such as those set forth in Farazi et al. and Roelant et al.

Applicant respectfully traverses. Applicant asserts that no motivation existed for a person skilled in the art to combine the cited references by performing cell proliferation assays using IMPDH mutated at residues 333 and 351. The Office Action states that the motivation for mutating residues 333 and 351 in the IMPDH of Farazi et al. was to "make and screen for other mutant human IMPDH which are resistant to IMPDH inhibitors." The Office Action goes on to state that the motivation for performing cell proliferation assays was to "determine if said mutant IMPDH are resistant to IMPDH inhibitors." These statements assume that a person skilled in the art would be motivated to determine whether a mutant IMPDH was resistant to IMPDH inhibitors. However, the Office Action fails to disclose why a person skilled in the art would be motivated to do this. The only reason provided in the cited references for making such a determination appears to be set forth by Farazi et al. Farazi et al. teach inserting IMPDH mutants into *E. coli* cells and screening for IMPDH inhibitor resistance for one purpose only: "to identify the structural features that determine the species selectivity of MPA" (Farazi, abstract). Thus, a person skilled in the art who drew their motivation from Farazi et al. would set out to screen IMPDH mutants for this same purpose. Given this, such a person would only be interested in mutating those IMPDH residues that varied from species to species. However, Farazi et al. states "Recent mutagenesis experiments suggest that resistant results from the alteration of Thr<sup>333</sup>... *This residue is strictly conserved in all IMPDHs sequenced to date, and therefore cannot be a determinant of species selectivity*" (Farazi et al., p. 961, last paragraph – p. 962, first

paragraph, emphasis added). This statement is echoed by Lightfoot et al., which states "The threonine residue at position 333 is conserved across all species sequenced to date" (Lightfoot et al., p. 161, first paragraph). The fact that references can be combined does not render the resultant combination obvious unless the references also suggest the desirability of the combination (MPEP 2143.01). By making it clear that mutation of residue 333 would do nothing to elucidate structural determinants of species selectivity, Farazi et al. actually suggests that combining its teachings with the IMPDH mutant of Lightfoot et al. would be undesirable. Thus, a person skilled in the art would have no motivation to screen an IMPDH mutant containing mutations at residues 333 and 351 for IMPDH inhibitor resistance, because such a screen would do nothing to elucidate the structural features of species selectivity. No other reason for combining the references is provided by the Office Action.

Applicant further asserts that the cited references do not teach each and every element of the claimed invention. Specifically, the cited references do not teach the introduction of a nucleic acid encoding an altered human IMPDH into a *eukaryotic* cell in order to bring about an increase in proliferation and/or viability of the cell. Farazi et al. teach the introduction of altered IMPDH into *E. coli* cells, but they do not teach the introduction of altered IMPDH into eukaryotic cells. Lightfoot et al. teach the identification of a eukaryotic cell line containing an altered IMPDH, but they do not teach the insertion of this altered IMPDH into a cell. There is no teaching or suggestion in either reference to combine the references and insert an altered IMPDH into a eukaryotic cell. As stated above, at the time the present application was filed, no motivation existed for one skilled in the art to screen an IMPDH mutant containing

mutations at residues 333 and 351 for IMPDH inhibitor resistance. Thus, no motivation existed for one skilled in the art to combine the Farazi et al. and Lightfoot et al. references.

In light of the foregoing, Applicant respectfully requests that the obviousness rejection be reconsidered and withdrawn.

**CONCLUSION**

In view of the foregoing, it is submitted that the present claims are in condition for allowance. Accordingly, Applicant respectfully requests that a Notice of Allowance be issued.

Respectfully submitted,  
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